## Detailed Action

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 12/28/07 has been entered.

## Election/Restriction

Claims 13-22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 2/13/06.

## Substitute Specification

The Substitute Specification filed 1/22/08 is acceptable and has been entered.

## 35 USC 112, 1st Paragraph Rejections

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection is maintained for reasons of record in the previous Office Action (Mailed 11/30/06). Applicants have amended clam 23 to delete the word "the" prior to the phrase "200 base pair fragment" and replaced it with “a” as well as deleting the word “adjacent” and replacing it with “proximal”. The specification provides support for the term "proximal" but in the context of **the 200 base pair promoter sequence proximal to the start codon of the relA/SpoT coding sequence**. Claim 23, as amended, now reads on any 200 base pair sequence upstream and proximal to the Mycobacterium tuberculosis relA/SpoT **gene**. The term “gene” is art recognized as including the coding sequence and the 5' (i.e. promoter) and 3' regulatory regions which regulate expression of the coding region. A reasonable interpretation of the claim reads on a 200 base pair sequence upstream and proximal to the **entire relA/SpoT gene**, which reads on a 200 base pair promoter sequence upsteam and proximal to the promoter and any additional 5' regulatory regions of the relA/SpoT gene. In summary, Claim 23 recites **any** 200 bp promoter fragment upstream and proximal to the *M. tuberculosis* relA/SpoT gene, while the instant specification provides support **only for the 200 bp sequence upstream and proximal to the start codon of the relA/SpoT coding region and specifically the sequence of SEQ ID NO:2**. This is a NEW MATTER rejection.

**35 USC 103(a) Rejections**

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Avarbock et al. in view of Ojha et al.

Applicants claim a *Mycobacterium* promoter, wherein the promoter is stable in *M. smegmatis* and *E. coli*, and consists of a 200 base pair fragment upstream and proximal to the *Mycobacterium tuberculosis* relA/SpoT gene. Applicants, in the instant specification, note that the relA/SpoT homologue in *M. tuberculosis* had been cloned and expressed by the inventors and that a 1.5Kb upstream fragment of the rel gene had been cloned (see paragraph [0013] of the instant specification, numbered as per the PG publication 2005/0085252).

Avarbock et al. (Gene, 1999, Vol. 233, pp. 261-269, see whole article, particularly the Abstract, Figs. 1-2, Discussion section on p. 266, etc.) teaches the cloning and characterization of the relA/SpoT homologue in *M. tuberculosis*. Avarbock et al. cloned the upstream and downstream sequences of the relA/SpoT homologue in *M. tuberculosis* (see Fig. 2) and compared the gene organization of the *rel* locus in *M. tuberculosis* with that of multiple other organisms. Avarbock et al. indicates that the relA/SpoT promoter appears to be located in the intergenic region immediately

upstream of the relA/SpoT coding region and in the upstream *apt* gene. Avarbock et al. does not provide a specific rationale for isolating the promoter of the relA/SpoT gene.

Ojha et al. (Infection and Immunity, 2000, Vol. 68, No. 7, pp. 4084-4091, see whole article, particularly the 2nd paragraph of the "Materials and Methods" section on p. 4085, pp. 4089-4090, etc.) teaches that the relA/SpoT gene products are involved in production of ppGpp and that ppGpp may play an important role in latency in mycobacteria and that studies on the stringent pathways (involving accumulation of ppGpp) may be important in understanding the transformation of avirulent to virulent forms of *M. tuberculosis*.

The prior art indicates that the relA/SpoT gene from *M. tuberculosis* had been cloned and expressed. The upstream promoter region had been characterized to some extent (see Fig. 2 of Avarbock et al.). Applicants themselves indicate that the upstream region of the relA/SpoT gene of *M. tuberculosis* had been cloned. The question therefore is whether it would have been obvious for the ordinary skilled artisan to isolate the promoter region of the *M. tuberculosis* gene. The answer must be yes because the relA/SpoT gene is involved in the important stringent response (see Ojha et al.) and characterization of the promoter of this gene would be important in understanding the importance of this response in determining *M. tuberculosis* virulence. The next question is whether a 200 bp fragment of the proximal upstream region would have been the obvious promoter region. The answer again must be yes because the gene organization of the *rel* region from several species including *M. tuberculosis* had been characterized and the promoters of relA/SpoT genes in other species had been found

within the approximately 200 bases upstream of the coding region (see Avarbock et al., p. 266, right column, citing Chakraburtty et al.). Indeed, Avarbock et al. indicates the promoter for the relA/SpoT gene from *M. tuberculosis* is probably within the 30 bp intergenic gene between the relA/SpoT gene and in the *apt* gene and that readthrough transcription from the *apt* gene probably also occurs, as had been shown in *S. coelicolor*.

The ordinary skilled artisan therefore would have been motivated to isolate the *M. tuberculosis* relA/SpoT promoter in the 200 base pair upstream proximal region to the relA/SpoT ORF because the genomic organization of the relA/SpoT gene region had been characterized and the promoter regions of other relA/SpoT genes had been found in approximately 200 bases upstream of the relA/SpoT ORF (see Avarbock et al.) and because analysis of the promoter of the relA/SpoT gene is important in understanding regulation of the stringent response of *M. tuberculosis* and possibly could be relevant in regulating transformation of *M. tuberculosis* from avirulent to virulent forms. It would have been obvious for the ordinary skilled artisan to isolate the 200 bp promoter fragment from the *M. tuberculosis* relA/SpoT gene because the relA/SpoT gene was known and the promoter region outlined and because the relA/SpoT gene was believed to be relevant to the stringent response and possibly the transformation of *M. tuberculosis* from avirulent to virulent forms and therefore analysis of the properties of the promoter would be useful. Given the nature of the prior art and the level of skill of the ordinary skilled artisan at the time of applicants' invention, the ordinary skilled

artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claims 24-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Avarbock et al. in view of Ojha et al. as applied to claim 23 above, and further in view of Hemming et al.

Applicants' invention is as described above. In addition, applicants recite that the promoter is operatively linked to a reporter gene which can be LacZ or xylE (catechol dioxygenase) and that the promoter is contained in a plasmid with an ampicillin or kanamycin resistance marker. Also, the promoter is recited as being 2.5 fold more active in *M. smegmatis* than a heat shock protein 60 promoter, $P_{hsp60}$.

Avarbock et al. and Ojha et al. are applied as in the above 103(a) rejection of claim 23. Neither reference teaches that the *M. tuberculosis* relA/SpoT promoter is operatively linked to a reporter gene which can be LacZ or xylE (catechol dioxygenase) and that the promoter is contained in a plasmid with an ampicillin or kanamycin resistance marker.

Hemming et al. (US 4,753,876, see whole document, particularly the "Marker Genes" section in columns 1-2, column 8, etc.) teaches that marker (reporter) genes are useful for studies of gene expression and that said markers can be LacZ or catechol dioxygenase (xylE) and that plasmids containing said makers can also include antibiotic resistance markers such as a kanamycin resistance marker.

The ordinary skilled artisan, seeking to analyze the characteristics of the relA/SpoT promoter would have been motivated to operably link said promoter to a reporter such as LacZ or xylE and include the promoter-marker gene in a plasmid comprising an antibiotic resistance marker such as $Kan^+$ because marker genes have been widely used to study gene expression and antibiotic resistance markers have likewise been widely used to select for cells comprising the plasmids. It would have been obvious for the ordinary skilled artisan to do this because use of reporters and antibiotic resistance markers was extremely well known in the gene expression art (as exemplified by Hemming et al.) and was widely used in the analysis of promoter characteristics. Given the nature of the prior art and the level of skill of the ordinary skilled artisan at the time of applicants' invention, the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

With regard to the limitation that the promoter is recited as being 2.5 fold more active in *M. smegmatis* than a heat shock protein 60 promoter, $P_{hsp60}$, it is noted that this appears to be an inherent feature of the *M. tuberculosis* relA/SpoT promoter and hence would not be an unexpected result.

Claim 29 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any rejections not repeated in this Office Action are withdrawn.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo, Ph.D., whose telephone number is (571) 272-0767. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D., can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

February 29, 2008

/David Guzo/
Primary Examiner
Art Unit 1636